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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER
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Commissioner for Patents

Enclosed, please find a corrected copy of the examiner's answer and an intialed and signed Information Disclusure Statement (IDS), filed October 11, 2005. The correction to the examiner's answer mailed 8/19/2004 was requested by the Board because the list of references cited in the rejection was inadvertanly missing from the orginal examiner's answer.

Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit: 1656

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/686,497
Filing Date: October 11, 2000
Appellant(s): SELDEN ET AL.

Laurie Butler Lawrence
For Appellant

EXAMINER'S ANSWER

CORRECTED

This is in response to the appeal brief filed June 30, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences, which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The brief contains a statement that the claims should stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) **Evidence Relied Upon**

WO 96/09378 Seed 3/1996

Kim et al. Gene 199, 293-301 (1997).

Morgan et al. Pediatr. Nephril 1, 536-539 (1987).

Bishop et al. Proc. Natl. Acad. Sci. USA 83, 4859-4863 (1986).

Wada et al. Nucleic Acid Res. 20, 2111-2118 (1992).

(10) Grounds of Rejection

Claims 1-14 and 26-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Seed [IDS (paper number 12): Ref. AG: WO 96/09378] in view of the prior art as exemplified by Kim *et al.* [IDS (paper number 4): Ref AQ: Gene 199, 293-301 (1997)], Morgan *et al.* [Pediatr. Nephrol. (1987) 1, 536-539], Bishop *et al.* [Proc. Natl. Acad. Sci. U. S. A. (1986), 83, 4859-4863], and Wada *et al.* [Nucleic Acid Research 20, 2111-2118 (1992)].

Seed teaches a synthetic mammalian gene in which at least one non-preferred or less preferred codon is replaced with a mammalian preferred codon, see page 1, lines 20-26. The preferred codons are taught on page 1, lines 27-32. He teaches that said modified mammalian gene is expressed at much higher level which is 110%, 150%, 200%, 500%, 1000% or 10,000% relative to that of the wild-type mammalian gene, see page 2, lines 10-16. Also, he teaches a method of preparing the nucleic acid in which the non-preferred or less preferred codon are identified in a natural gene and replaced by a preferred codon encoding the same amino acid, see page 3, lines 8-14. The mammalian gene could encode any desired protein or fragment thereof having any length, see page 4, line 3-9. Seed does not teach a synthetic gene encoding human α-galactosidase.

Kim *et al.* teach that selective codons in a given gene positively correlate with its expression efficiency, see abstract. Also, they teach the codon optimization of a leader sequence leads to further enhancement of a synthetic gene, see page 297, right column, section 3.3.

Morgan *et al.* teach that Anderson-Fabry disease is an X-linked lysosomal storage disorder due to α-galactosidase A deficiency, see abstract.

Bishop *et al.* teach the cDNA encoding human α-galactosidase A, see Figure 2, and that mutation in the DNA encoding the enzyme causes Fabry disease, see the paragraph bridging the left and right columns on page 4859.

Wada *et al.* teach the common codon used by many organisms.

Morgan *et al.* provides one of ordinary skill in the art with motivation to develop a method for making α-galactosidase to use for the treatment of Anderson-Fabry disease as they teach Anderson-Fabry disease is caused by deficiency in human α-galactosidase A. Seed and Kim further motivate the ordinary skill in the art to synthesize α-galactosidase in which the non-common and less common codons are replaced with common codon for mammalian cells to enhance the expression of α-galactosidase A in said cells. Thus, it would have been obvious to one of ordinary skill in the art to identify the less-common and non-common codon used for mammalian cells in a gene encoding α-galactosidase such as the human α-galactosidase A taught by Bishop *et al.* (12-14), synthesize the codon optimized gene (claims 1-8 and 26-32), construct a mammalian expression vectors comprising the synthetic gene (claim 9), transform a mammalian cell with said vector (claim 10), and express the synthetic gene in a mammalian cell of choice as taught by Seed and Kim *et al.* to make the desired α-galactosidase (claim 11). It should be noted that the ordinary skill in the art would have been motivated to change every single less common

and non-common codon to a common codon to optimize the level of expression of the desired α-galactosidase in the host cell so the resulting sequence could be 100% common codons (claims 1-8 and 26-32). Also, applicants should note that any α-galactosidase gene from any biological source can be optimized for express in almost any host cell including human, *E. coli*, yeast, and insect among others because the common codons for many organisms are known, see Wada *et al.* Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

(11) Response to Argument

(I) Appellants admitted on record that the examiner has established a *prima facie* case of obviousness.

On page 4 of the brief, second paragraph, appellant have made a distinction between generally optimize gene and very high levels of optimization. They argue that the references, singly and in combination, fail to suggest any gene, much less the specifically claimed gene (human α-galactosidase), having the high levels of common codons required by the claims.

Appellants' arguments filed June 3, 2004 have been fully considered, but they are found unpersuasive. The examiner does not understand the difference between "generally optimize gene" and "very high levels of optimized gene". It seems the appellants are trying to argue the level of optimization taught in the prior art is different from that of the instant application. Such an argument is incompatible with the prosecution history of the application and the teaching of the prior art of record. In response to the final Office action filed October 24, 2003, Appellants admitted on record that the examiner has established a *prima facie* case of obviousness, see page 6, paragraph 3. Thus, the appellants consider that the prior art provide sufficient technical teaching of the claimed invention as well as motivation, and expectation of success to one of ordinary skill in the art. Now, it appears that the appellants have changed their mind

regarding the teaching of the prior art. They provide their new understanding of the teaching of prior art of Seed and Kim. In the last paragraph on page 4 of the brief, appellants states:

> "Seed teaches a synthetic gene encoding a protein normally expressed in mammalian cells wherein at least one non-preferred or less preferred codon in the natural gene encoding the mammalian protein has been replaced by a preferred codon encoding the same amino acid (see Abstract). However, Seed provides only a generalized description of optimized nucleic acid sequences that neither teaches nor suggests sythetic sequences (much less α-galactosidase sequences) with the very high level or range of common codons required by the claims."

While Seed does not teach the optimized or highly optimized human α-galactosidase, it teaches highly optimized gene normally expressed in human cells, i. e, HIV-1 gp120 and another gene normally expressed in jellyfish. On page 12, he writes:

> "In order to produce a gp120 gene capable of high level expression in mammalian cells, a synthetic gene encoding the gpl20 segment of HIV-I was constructed (syngp120mn), based on the sequence of the most common North American subtype, HIV-I MN (Shaw et al., Science 226:1165, 1984; Gallo et al., Nature 321:119, 1986). In this synthetic gp120 gene nearly all of the native codons have been systematically replaced with codons most frequently used in highly expressed human genes (FIG. 1). This synthetic gene was assembled from chemically synthesized oligonucleotides of 150 to 200 bases in length. If oligonucleotides exceeding 120 to 150 bases are chemically synthesized, the percentage of full-length product can be low, and the vast excess of material consists of shorter oligonucleotides." (Underline added for emphasis)

Clearly, the above passage indicates that changing all the non-preferred codon with preferred codons are within the invention taught by Seed. Seed's teaching is detailed in describing the construction of the synthetic genes from several chemically synthesized fragments; see Figure 1 and page 12, line12 through page 14, line 30. On page 25, lines 13-26, he states unequivocally that:

> "The systematic exchange of native codons with codons of highly expressed human genes dramatically increased expression of gp120. A quantitative analysis by ELISA showed that expression of the synthetic gene was at least 25 fold higher in comparison to native gp120 after transient transfection into human 293 cells. The concentration levels in the ELISA experiment shown were rather low. Since an ELISA was used for quantification, which is based on gp120 binding to CD4, only native, non-denatured material was detected. This may explain the apparent low expression. Measurement of cytoplasmic mRNA levels demonstrated that the difference in protein expression is due to translational differences and not mRNA stability."

Thus, the teaching of Seed is sufficiently detailed to guide one of ordinary skill in the art construct a synthetic gene in which all or the vast majority of the human non- and un-preferred codons are substituted with the human preferred codons.

Appellants argue on page 6 of the brief that the enhanced expression of an optimized gene encoding gp120 in human cell is not germane to the present claims because gp120 is not a human gene. They continue to argue that:

> "In contrast, the claims recite replacing non-preferred codons in a particular human sequence (one encoding human alpha-Gal A) with common human codon. This is completely different concept than replacing codons in a non-human sequence with common human codons."

Appellants' arguments have been fully considered, but they are found unpersuasive. The arguments presented by the applicants raise several questions.

(i) Does the source of the gene impart a special technical problem to one of ordinary skill in the art?

(ii) Is the source of the gene relevant?

(iii) Is a naturally isolated gene "optimized" for expression in its native cell, in particular, human gene in a human cell?

The answer to all three questions is unqualified no. The prior art of record as well as the state of the art show that any gene from any source can be expressed in any cell at high level. Human genes can be expressed successfully in about any prokaryotic cells and eukaryotic cell including yeast and human cells, as well as expressing prokaryotic genes in eukaryotic cells. Neither the prior art of record or the specification provide any special problems associated with human gene in general, or human alpha-Gal A in particular. Seed teaches the optimization of at least two genes from the human immunodeficiency virus type-1 (HIV-1) and jellyfish to express in human cells at high level by replacing non- and un-preferred human codons with preferred human codons. HIV-1 gp120 gene is naturally expressed only in infected human cells and thus, would be expected to be evolved for expression in human cells. Since highly expressed human genes display preferences for CpG codons, any optimized gene from any biological source including human will contain an increased number of the CpG codons. Thus, the source and the identity of the gene are irrelevant to the optimization process, and the end result is the same. At the end, when a gene is optimized to high level of expression in human cells as taught by Seed, it will have higher levels of CpG dinucleotide than the native sequence.

Appellants would like us to believe "human sequence has been already optimized by nature", see page 6 of the brief, lines 8 and 9 from the bottom of the page. This is simply not true. There is no evidence of record to support

appellant allegation. While it is intuitive that genes from a given organism is optimized for expression in its native cell at certain level to meet the organism need of said gene product, said gene is not definitely optimized for maximum expression in its native cell. Over expression or under expression of a gene in its native cell may have a long-term undesired effects on the organism. It is worth noting that the Kim reference, which is discussed bellow, have shown that a human gene can be optimized for expression in human cell by substituting the vast majority of the non- and un-preferred human codons to preferred human codons. Thus, one of ordinary skill in the art would recognize that the human alpha-Gal A gene taught by Bishop *et al.* is not naturally optimized for maximum expression in human cells because it contains large number of non- and un-preferred codons.

(II) The prior art teaching a way from the invention is an element to be considered in an obviousness type rejection, but it is not the only factor to be considered.

Appellants argue that Seed and Kim teach away from the claimed invention because they caution against substantial increased use of CpG. They continue to argue, "Given the teaching of Seed, such a modification, at the time the application was filed, would have predicted to cause gene silencing, as explicitly stated in Seed."

Appellants' arguments have been fully considered, but they are found unpersuasive. It is true that both Seed and Kim have cautioned against large number of CpG dinucleotide in the synthetic gene, see Seed, page 5, lines 1 and 2; and Kim page 299, right column last paragraph. In contrast, neither reference teaches that any increase in the CpG content would lead to silencing the gene. Despite their cautionary remarks, both Seed and Kim went a head and optimized heterologus and human genes to be expressed in human cells by replacing the vast majority of the human non- and un-preferred codons with human preferred

codons. Both reference teach synthetic genes containing substantial increase in the CpG dinucleotide content, and have not reported any silencing of any synthetic genes. In addition, both references report substantial increase of expression for the optimized gene in human cells. In particular, Table 1 on page 11 of the Seed reference compare codon frequency in the HIV-1 IIIb envelope gene and those in highly expressed human genes. It shows that the retroviral envelope gene displays large preference for codons with A in the third position, whereas those of human codons ending with C or G are the most preferred. So, the synthetic gene taught by Seed, contained much higher levels of the CpG than that of the wild type, yet it is expressed at least 25 fold more than the wild-type gene in human cell. Thus, the experimental results point to the fact that human cells have been developed the means to express genes with high CpG content.

Appellants content that the mere presence of cautions in the reference(s) leads away from substantial increased use of CpG pairs. The appellants continue to argue, "Given the teaching of Seed, such a modification have been predicted to cause gene silencing. While these cautionary remarks must be considered, it has to be considered and weighted against objective evidence of record. Section 716.01(d) of the MPEP provides the examiner with guidance in determining patentability and states:

> "IN MAKING A FINAL DETERMINATION OF PATENTABILITY, EVIDENCE SUPPORTING PATENTABILITY MUST BE WEIGHED AGAINST EVIDENCE SUPPORTING PRIMA FACIE CASE."

Also, MPEP section 2145 (D) states:

> "In addition to the material below, see MPEP § 2141.02 (prior art must be considered in its entirety, including disclosures that teach away from the claims) and MPEP § 2143.01 (proposed modification cannot render the prior art unsatisfactory for its intended purpose or change the principle of operation of a reference)."

In re Hauruna, quoted by the appellants, is compatible with the teaching of the MPEP cited above in that it affirming the requirement of considering the teaching of the reference as a whole.

In the instant case, both reference provided the cautionary remark, but they went a head and substantially increased CpG dinucleotide in their synthetic gene relative to the wild type any way, and achieving spectacular results. The cited prior art of record contains preponderance of evidence in support of the *prima facie* case of obviousness. It teaches three synthetic genes with optimized human codons for expression in human cells, which resulted in substantial increase in their level expression in human cells despite of having substantially large increase in the levels of CpG dinucleotide, see the discussion above. The success of the prior art can't be ignored. It provides an adequate teaching on how to make the optimized synthetic genes and the expectation of success for increasing the expression of an optimized gene in human cells despite the increase in the number of CpG pair. A cautionary remark in the prior art, which the authors of the prior art acted against, does not rise to the same level of experimental results. Thus, one of ordinary skill in the art would have considered the cautionary remarks of Seed and Kim in view of their spectacular successes in the laboratory, and carry out the claimed invention any way.

(III) The Kim reference

The Kim reference is relied upon for the teaching that the expression of a native human gene can be highly optimized by replacing the non- and un-prefered codone with preferred codones. In spite of the increased content of CpG dinuclutide in the synthetic gene relative to the wild type human gene, the synthetic gene is expressed at high levels in human cells. Figure 2 on page 295 of Kim teaches the optimized sequence of the human coding sequence of the mature human erythropoientin (EPO). In the vast majority of the codons changes resulted in the substitution with G or C leading to increase the content of the CpG

pair. Apparently, appellant characterize the replacement of less than a 94% of the codons is "replacing only some". Clearly, Kim teach the expression of the human optimized EPO gene without the coding sequence for the signal peptide with human preferred codons and compared to the level of expression with that optimized with preferred codons for yeast (yeast prefer A in the third position of the codon). The synthetic EPO gene optimized for human cell expression contained 44 CpG, whereas the wild type EPO contained only 19. They report the expression of the synthetic gene optimized with human preferred codons expressed at higher levels than that optimized with yeast codons, see the paragraph bridging the two columns on page 297. Thus, even more the doubling the CpG has not deter the synthetic gene from expressing in human cells at high levels. Also, Kim compare the expression of two constructs comprising the mature protein coding sequence optimized with the human preferred codons with the coding sequence of the wild type EPO signal peptide and that wherein the coding sequence of the signal peptide is optimized with the yeast preferred codons. The result shown in Figure 7 indicates that the signal peptide play a role in the expression of the whole gene. Since the gene optimized with human codons in human cell expresses at a higher level than that optimized with yeast codons, the ordinary skill in the art would have come to the conclusion that optimizing the signal peptide coding sequence with human codon would enhance the expression even further.

Appellants argue: The EPO coding sequence of Kim includes at least the following amino acids encoded by non-common human codons: P2, P3, R4, L5, R14, C33, P87, P121, P122, and A124. For example, the most common codon encoding proline (P) in highly expressed human genes is CCC (see Fig. 1 of Kim and Table 1 of the present specification). However, the EPO coding sequence shown in Fig. 2 of Kim uses the codons CCA (P2, P3 and P87) and CCG (P121 and P122). Kim states that "[s]ome deviations from strict adherence to prevalent codon usage were made to accommodate the introduction of unique restriction

sites or to avoid homopolymeric DNA seguences" (Kim, page 297, first column). Kim thus teaches away from replacing codons with human common codons where the resulting sequence would contain repeated consecutive nucleotides", see the first paragraph on page 9 of the brief.

Appellants' arguments have been fully considered, but they are found unpersuasive. Appellants' claims are not limited to an optimized gene wherein 100% of the codons of human α-galactosidase gene are replaced with preferred codons. Claim 1 of the appealed claims is directed to at least 150 contiguous preferred codons, at least 60% of the codons are contiguous preferred codons, or 94% of the codons in the sequence are common codons. These limitations in claim 1 provide for the deviation from the strict adherence to prevalent codon usage to provide for the introduction of restriction site and avoid homopolymeric DNA sequences. Appellants appear to have identified at least 10 codons, which are not common codons in the optimized sequence with human codons. That is commendable feet, but 10 residues are only 6% of the codon in the synthetic gene and level of optimization fall within the limitation of claim 1 (94% of the codones aresubstituted with preferred codons). Whether the actual teaching of the Kim reference is a synthetic gene wherein 85%, 90%, 94%, or 100% of the codons are human preferred codones is a minor diversion. The real issue in this case is that Kim teaches the optimization of the expression of a human gene in human cells by substituting the vast majority of the non- and un-preferred codons with preferred codons in a human gene, which would be expected to increase CpG dinucleotide in the synthetic gene. Taken the result of Kim and Seed together, one of ordinary skill in the art would have come to the conclusion that any gene from any biological source including human can be optimized for expression in human cells by replacing the human non- and un-preferred codons with human preferred codons. The ordinary skill in the art would have had the teaching of Seed and Kim to make a synthetic gene, the expertise to carry out the claimed invention, the motivation to make human α-galactosidase in large

quantity, and the expectation of success. Thus, a *prima facie* case of obviousness is established, and could not be overcome by applicants' arguments because of the evidence taught in the prior art of record.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1652

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November 21, 2005

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